

Colchicine Therapy and Plaque Stabilization in Patients With Acute Coronary Syndrome

A CT Coronary Angiography Study



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ABSTRACT

OBJECTIVES The authors sought to evaluate the plaque-modifying effects of low-dose colchicine therapy plus optimal medical therapy (OMT) in patients post-acute coronary syndrome (ACS), as assessed by coronary computed tomography angiography (coronary CTA).

BACKGROUND Colchicine therapy has been postulated to have beneficial anti-inflammatory effects in patients with ACS, translating into reduction in future adverse cardiovascular events. However, whether favorable plaque modification underpins this is yet unproven.

METHODS In this prospective nonrandomized observational study of 80 patients with recent ACS (<1 month), patients received either 0.5 mg/day colchicine plus OMT or OMT alone and were followed for 1 year. Our primary outcome was change in low attenuation plaque volume (LAPV), a marker of plaque instability on coronary CTA and robust predictor of adverse cardiovascular events. Secondary outcomes were changes in other coronary CTA measures and in high-sensitivity C-reactive protein (hsCRP).

RESULTS Mean duration of follow-up was 12.6 months; mean age was 57.4 years. Colchicine therapy significantly reduced LAPV (mean 15.9 mm³ [−40.9%] vs. 6.6 mm³ [−17.0%]; $p = 0.008$) and hsCRP (mean 1.10 mg/l [−37.3%] vs. 0.38 mg/l [−14.6%]; $p < 0.001$) versus controls. Reductions in total atheroma volume (mean 42.3 mm³ vs. 26.4 mm³; $p = 0.28$) and low-density lipoprotein levels (mean 0.44 mmol/l vs. 0.49 mmol/l; $p = 0.21$) were comparable in both groups. With multivariate linear regression, colchicine therapy remained significantly associated with greater reduction in LAPV ($p = 0.039$) and hsCRP ($p = 0.004$). There was also a significant linear association ($p < 0.001$) and strong positive correlation ($r = 0.578$) between change in LAPV and hsCRP.

CONCLUSIONS Our findings suggest, for the first time, that low-dose colchicine therapy favorably modifies coronary plaque, independent of high-dose statin intensification therapy and substantial low-density lipoprotein reduction. The improvements in plaque morphology are likely driven by the anti-inflammatory properties of colchicine, as demonstrated by reductions in hsCRP, rather than changes in lipoproteins. Colchicine may be beneficial as an additional secondary prevention agent in patients post-ACS if validated in future studies. (J Am Coll Cardiol Img 2018;11:305–16)

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Manuscript received May 2, 2017; revised manuscript received August 3, 2017, accepted August 4, 2017.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CAD = coronary artery disease

CV = cardiovascular

CVD = cardiovascular disease

CTA = computed tomography angiography

DCPV = dense calcified plaque volume

hsCRP = high-sensitivity C-reactive protein

HU = Hounsfield units

IL = interleukin

LAP = low attenuation plaque

LAPV = low attenuation plaque volume

LDL = low-density lipoprotein

MACE = major adverse cardiovascular events

NCPV = noncalcified plaque volume

OMT = optimal medical therapy

TAV = total atheroma volume

TC = total cholesterol

Inflammation plays a pivotal role in all stages of atherosclerotic plaque development, including promotion of plaque instability and acute coronary syndrome (ACS) presentation. In the coronary vasculature, inflammation is not localized to the culprit stenosis; persistent inflammatory cell activation has been demonstrated at sites remote from an index plaque rupture. This may lead to recurrent plaque rupture and cardiovascular (CV) events, despite optimal medical therapy (1,2).

Colchicine is a commonly used anti-inflammatory medication that prevents mitosis via inhibition of microtubule polymerization (3-5). Low-dose colchicine has been proven to be safe, well tolerated, inexpensive, and readily available. There is increasing evidence supporting a potentially beneficial role for colchicine therapy in prevention of cardiovascular disease (CVD). Our group has recently shown that short-term colchicine administration in patients with ACS significantly reduces systemic and local transcoronary production of inflammatory cytokines implicated in atherosclerosis (3). However, it is unknown whether these cytokine changes translate into favorable plaque modification.

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Coronary computed tomography angiography (coronary CTA) is a noninvasive imaging modality that not only detects significant coronary artery anatomic stenoses, but also allows detailed examination of coronary plaque composition. Specific plaque morphologies on coronary CTA are suggestive of vulnerability to rupture and are associated with future ACS events, such as low attenuation plaque (LAP), positive remodeling, spotty calcification, and the “napkin ring” sign. Of these, LAP has been consistently shown to be the best marker of instability and strongest prognostic predictor of a future adverse CV event (6,7). Although a number of studies have used serial coronary CTAs to assess plaque progression and changes in morphology after a specific intervention, such as statin therapy, this has never been performed with colchicine. We therefore undertook this prospectively designed pilot study to investigate whether colchicine therapy could reduce certain adverse plaque characteristics, as assessed by coronary CTA.

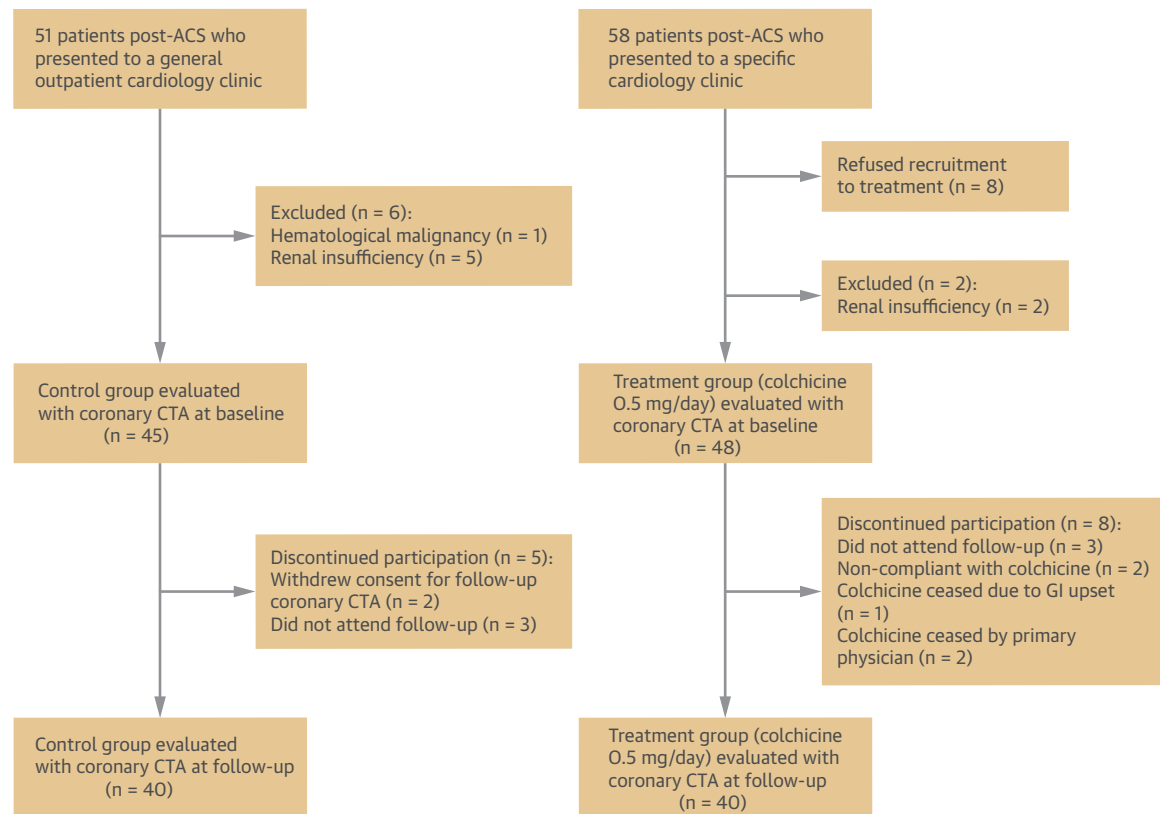
METHODS

STUDY DESIGN AND RECRUITMENT. This was a prospective, open-label, single center study at Royal Prince Alfred Hospital examining the effect of 12 months of colchicine therapy on coronary plaque morphology in patients who had recently presented (<1 month) to the hospital with an ACS (8) (Figure 1). All patients underwent invasive coronary angiography at the time of presentation and were revascularized if clinically indicated. Between January 2015 and March 2016, 48 patients were recruited from a specific cardiology clinic at our institution. These patients underwent coronary CTA and were routinely started on colchicine (0.5 mg/day). Forty patients in this treatment arm completed the study. The control arm initially consisted of 45 patients, recruited between December 2014 and October 2015 from a general cardiology outpatient clinic at the same institution; 40 patients from this arm completed the study. In both groups, all patients underwent statin and risk factor optimization at the discretion of their treating cardiologist. Because the presence of LAP on coronary CTA has been shown to be a robust predictor of future major adverse cardiovascular events (MACE), we chose change in LAP volume (LAPV) at follow-up in colchicine-treated versus nontreated patients as the primary study endpoint. The secondary endpoints were changes in other coronary CTA measures: total atheroma volume (TAV), noncalcified plaque volume (NCPV), dense calcified plaque volume (DCPV), remodeling index, and high-sensitivity C-reactive protein (hsCRP). The local Ethics Review Committee approved the study protocol and all patients gave written informed consent before participating.

EXCLUSION CRITERIA. We excluded patients with previous coronary artery bypass grafts, a hypersensitivity/allergy to colchicine, colchicine treatment for another cause, severe liver disease, renal insufficiency with creatinine clearance <45 ml/min, calcineurin or strong CYP3A4 inhibitor treatment, hematological malignancy, thrombocytopenia, leucopenia, chronic inflammatory bowel disease, pregnancy or at risk of pregnancy, and lactating women.

CLINICAL DATA AND LABORATORY MEASUREMENTS. Upon recruitment of patients, initial contact with investigators involved a comprehensive medical history, physical examination, medication evaluation, and anthropometric measurements. Blood samples were collected after an overnight 8 to 12 h fast. Samples were stored and subsequently analyzed for hsCRP, urea and creatinine, hepatic enzymes,

FIGURE 1 The Enrollment, Exclusion, and Follow-Up of Patients Post-ACS Recruited to the Control or Treatment Group



ACS = acute coronary syndrome; CTA = computed tomography angiography; GI = gastrointestinal.

low-density lipoprotein (LDL), total cholesterol (TC), high-density lipoprotein, and triglyceride levels with the use of automated diagnostic equipment.

FOLLOW-UP AND MONITORING. All patients were reviewed clinically at 3 and 12 months after enrollment for drug reactions, self-reported medication compliance (both statin and colchicine), and MACE. A follow-up period of 12 months for serial coronary CTA was chosen on the basis of prior studies (9,10) that assessed changes in plaque morphology after statin therapy.

CORONARY CTA DATA ACQUISITION. Coronary CTA was performed using a Discovery CT750 HD (GE Healthcare, Milwaukee, Wisconsin). The same protocol, image setting, and dose of contrast medium was used at both baseline and follow-up. Sublingual nitroglycerin and oral beta-blockers were administered pre-scan. The following imaging and reconstruction variables were applied: collimation 64.000×0.625 mm, tube voltage 100 to 120 kV, and tube current 350 to 780 milliamperes. Prospective studies were performed if the heart rate was

sufficiently controlled (<60 beats/min) with images acquired from 65% to 75% of the R-R interval. An iodinated contrast material (350 g/l) (Omnipaque, GE Healthcare) was injected intravenously.

CORONARY CTA CORONARY PLAQUE ASSESSMENT.

All coronary images were transferred to the workstation with the use of semiautomated plaque-based analysis software (GE Advantage workstation v4.5 cardiq express). Operators and observers were blinded for colchicine treatment or control group allocation, and experienced reporters assessed the coronary arteries. The protocol for quantitative plaque assessment has been published in previous studies (11), with 3-dimensional image reconstruction including volume rendering and curved multiplanar reformation. Vessel diameters ≥ 1.5 mm were evaluated and assessed based on a Society of Cardiovascular Computed Tomography 17-segment coronary artery model (12). Stented segments were excluded. A software-derived color-coded map overlay differentiated plaque categories by Hounsfield unit (HU) values. Parameters assessed included LAP (<30 HU), intermediate

TABLE 1 Baseline Characteristics of Control and Treatment Groups

	Control (n = 40)	Treatment (n = 40)	p Value
Age, yrs	58.4 ± 14.2	56.3 ± 8.9	0.42
Male	30 (75.0)	32 (80.0)	0.59
Diabetes mellitus	16 (40.0)	9 (22.5)	0.09
Hypertension	23 (57.5)	20 (50.0)	0.50
Tobacco smoking	21 (52.5)	20 (50.0)	0.82
Dyslipidemia	34 (85.0)	34 (85.0)	1.00
Previous MI	22 (55.0)	19 (47.5)	0.50
Previous PCI	23 (57.5)	28 (70.0)	0.25
Aspirin	40 (100.0)	38 (95.0)	0.15
Thienopyridine	29 (72.5)	33 (82.5)	0.28
Statin	38 (95.0)	32 (80.0)	0.04
BMI, kg/m ²	27.4 ± 3.3	26.6 ± 3.2	0.28
Follow-up period, months	12.9 ± 0.6	12.2 ± 3.9	0.27
Type of ACS	-	-	0.42
STEMI	6 (15.0)	3 (7.5)	-
NSTEMI	16 (40.0)	14 (35.0)	-
UAP	18 (45.0)	23 (57.5)	-
hs-Troponin T, ng/l	433.4 ± 958.1	318.3 ± 862.2	0.10
Type of treatment post-ACS	-	-	0.28
Medical only	7 (17.5)	11 (27.5)	-
PCI	33 (82.5)	29 (72.5)	-

Values are mean ± SD or n (%).

ACS = acute coronary syndrome; BMI = body mass index; hs = high-sensitivity; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UAP = unstable angina pectoris.

attenuation noncalcified plaques (30 to 150 HU), dense calcified plaques (DCP) (351 to 1,000 HU), total atheroma volume (TAV) (TAV = LAPV + NCPV + DCPV), and total lumen volume (TLV) (151 to 350 HU) (11). The volume of each component was measured. Percent LAP, NCP, dense calcified plaques, and TAV were defined as the volume of each parameter divided by total vessel volume (TVV) (TVV = TAV + TLV). Another measure of plaque instability was remodeling index, with a plaque remodeling

index >1.1 considered to be within a positive remodeled artery (6). To assess interobserver variability, LAP, NCP, dense calcified plaques, and lumen volumes on 15 randomly selected patients were independently assessed by 2 reporters. Excellent interobserver agreement was observed ($\kappa = 0.83$).

STATISTICAL ANALYSIS. Continuous variables are expressed as the mean ± SD; categorical variables are described as n (%). For univariate analysis, we used the Student *t* test to compare means between treatment and control groups for the normally distributed continuous variables: age, body mass index, follow-up period, baseline LDL, baseline TC, baseline TAV, and baseline NCPV. We used the Mann-Whitney *U* test for the remaining non-normally distributed (including outcome) variables. Comparison between groups for qualitative variables was performed using the chi-square or Fisher exact test as appropriate. We also performed a repeated measures 2-way mixed analysis of variance to determine if an interaction effect exists between treatment group (controls vs. colchicine) and time (baseline vs. follow-up) for the outcome variables. Spearman's rank order correlation coefficient (*r*) was used to evaluate the relationship between continuous outcome variables. To correct for differences between groups and to account for factors that may have influenced outcomes (particularly plaque morphology) during the follow-up period, we performed multivariate linear regression analysis. We adjusted for age, sex, body mass index, follow-up period, baseline LDL, comorbidities (diabetes mellitus, hypertension, dyslipidemia, tobacco smoking), and medication use (statin, aspirin, thienopyridines). We excluded 1 outlier (standardized residual 6.3 SDs from mean) for the change in hsCRP outcome only. A 2-tailed *p* value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 20.0 (SPSS Inc., Chicago, Illinois).

RESULTS

BASILINE CHARACTERISTICS. From December 2014 to March 2016, we enrolled 40 patients who were assigned to colchicine 0.5 mg/day plus optimal medical therapy (OMT) and 40 patients to OMT alone. All regular medications were continued, and high-dose statin intensification therapy (aiming for LDL <1.8 mmol/l) was initiated for 70 (87.5%) patients. Before enrollment, 39 (48.75%) patients were taking statin therapy (control: n = 18; treatment: n = 21). Mean duration of follow-up was 12.6 ± 2.8 months; the mean age of patients was 57.4 ± 11.8 years. We recruited 62 men (77.5%) and 18 women (22.5%).

TABLE 2 Baseline Coronary CTA Plaque Parameters Between Treatment and Control Groups

	Control (n = 40)		Treatment (n = 40)		p Value*
	Baseline (mm ³)	Baseline TVV* (%)	Baseline (mm ³)	Baseline TVV† (%)	
LAPV	39.0 ± 10.9	7.3 ± 2.0	38.8 ± 13.6	7.7 ± 2.7	0.37
DCPV	21.5 ± 11.8	4.0 ± 2.2	18.6 ± 10.1	3.7 ± 2.0	0.26
NCPV	185.0 ± 41.3	34.7 ± 7.7	181.6 ± 70.5	36.1 ± 14.0	0.79
TAV	245.5 ± 42.3	46.0 ± 7.9	239.0 ± 76.0	47.5 ± 15.1	0.64
TLV	287.9 ± 29.6	54.0 ± 5.5	264.2 ± 78.7	52.5 ± 15.6	-
RI	1.18 ± 0.16	-	1.20 ± 0.17	-	0.58

Values are mean ± SD. *Mean TVV = 533.4 mm³. †Mean TVV = 503.2 mm³. ‡p value comparing raw baseline values (mm³) between the 2 groups.

CTA = computed tomography angiography; DCPV = dense calcified plaque volume; LAPV = low attenuation plaque volume; NCPV = noncalcified plaque volume; RI = remodeling index; TAV = total atheroma volume; TLV = total lumen volume; TVV = total vessel volume.

TABLE 3 Baseline, Follow-Up, and Changes in Lipid and Biochemical Parameters in the Control and Treatment Groups

	Baseline			Control			Treatment		
	Control (mmol/l) (n = 40)	Treatment (mmol/l) (n = 40)	p Value*	Follow-Up (mmol/l) (n = 40)	Change (%) From Baseline (mmol/l)	p Value†	Follow-Up (mmol/l) (n = 40)	Change (%) From Baseline (mmol/l)	p Value‡
LDL	2.42 ± 0.49	2.33 ± 0.71	0.52	1.93 ± 0.50	−0.49 (20.2) ± 0.49	<0.001	1.89 ± 0.52	−0.44 (19.0) ± 0.60	<0.001
TC	4.83 ± 1.10	4.49 ± 1.27	0.20	3.90 ± 0.71	−0.93 (19.3) ± 0.87	<0.001	3.80 ± 1.12	−0.68 (15.2) ± 1.23	0.001
HDL	1.21 ± 0.17	1.20 ± 0.28	0.37	1.29 ± 0.23	+ 0.07 (5.8) ± 0.25	0.08	1.20 ± 0.24	−0.01 (0.6) ± 0.27	0.93
TG	1.75 ± 0.59	1.55 ± 0.71	0.09	1.66 ± 0.46	−0.10 (5.4) ± 0.47	0.24	1.39 ± 0.64	−0.16 (10.5) ± 0.47	0.04
	Control (mg/l) (n = 40)	Treatment (mg/l) (n = 39)		Follow-Up (mg/l) (n = 40)	Change (%) From Baseline (mg/l)		Follow-Up (mg/l) (n = 39)	Change (%) From Baseline (mg/l)	
hsCRP	2.64 ± 2.06	2.95 ± 1.56	0.26	2.26 ± 1.05	−0.38 (14.6) ± 1.21	0.02	1.85 ± 0.90	−1.10 (37.3) ± 1.15	<0.001

Values are mean ± SD or mean (%) ± SD. *p Value comparing baseline values between the 2 groups. †p Values comparing baseline and follow-up values in the ‡control group and the §treatment group. HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; TC = total cholesterol; TG = triglycerides.

Baseline characteristics (Tables 1 to 3) and comorbidities of the study population in the treatment and control cohorts were similar and well matched. The 2 groups differed only in use of a statin (p = 0.04). Complete data were available except for baseline hsCRP (control: n = 40; treatment: n = 39).

CHANGES AT FOLLOW-UP. Follow-up mean ± SD and changes in coronary CTA plaque parameters for treatment and control cohorts are summarized in Table 4. During the study period, there was a reduction in all coronary CTA plaque parameters of interest (LAPV, DCPV, NCPV, TAV), with statistically significant reductions in LAPV (treatment: p < 0.001; control: p = 0.003), NCPV (treatment: p = 0.005; control: p = 0.01), and TAV (treatment: p = 0.001; control: p < 0.001) in both groups. There was also a reduction in LAPV, NCPV, and TAV as a proportion of TVV in both groups; however, there was a small increase (+0.5%) in DCPV as a proportion of TVV in the treatment group, but not in the control group (−0.1%). There was a net reduction in LAPV at follow-up in 29 (72.5%) and 33 (82.5%) patients in the control and treatment groups, respectively. Figures 2 and 3 demonstrate how semiautomated coronary CTA

quantitative plaque analysis was performed in a treated patient at baseline and at 12-month follow-up.

During the study period, there was also a significant reduction (Table 3) in LDL (treatment: p < 0.001; control: p < 0.001), TC (treatment: p = 0.001; control: p < 0.001), and hsCRP (treatment: p < 0.001; control: p = 0.02) across both cohorts, and in triglycerides for the treatment group alone (p = 0.04). An increase in high-density lipoprotein was seen only in the control group; however, this change was not significant.

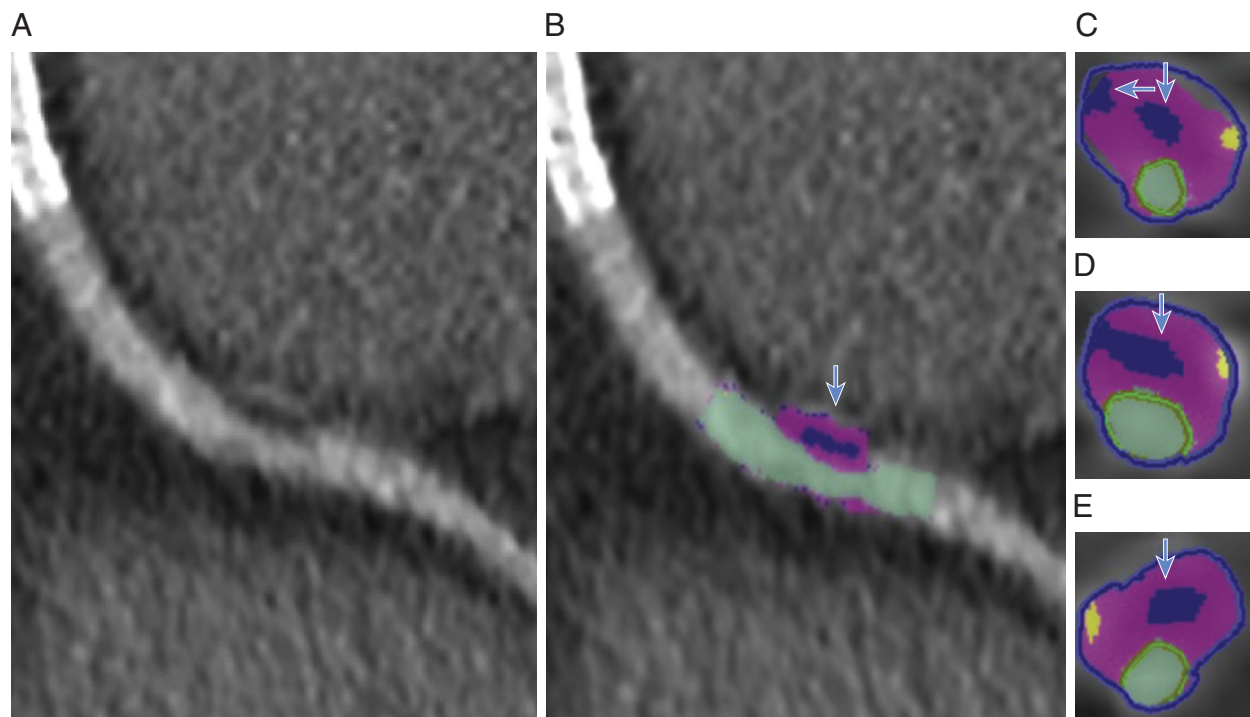
PRIMARY AND SECONDARY OUTCOMES. On univariate analysis (Tables 3 to 5), colchicine therapy was associated with a significant reduction in LAPV (treatment: mean 15.9 [−40.9%] ± 17.3 mm³; control: mean 6.6 [−17.0%] ± 12.8 mm³; p = 0.008) (Figure 4A) and hsCRP (treatment: mean 1.10 [−37.3%] ± 1.15 mg/l; control: mean 0.38 [−14.6%] ± 1.21 mg/l; p < 0.001) (Figure 4B) compared with the control group. Colchicine therapy (Tables 2 and 4) was associated with a mean 2.5% reduction in LAPV as a proportion of TVV versus a 1.0% reduction in the control group (p = 0.03).

Although there was a greater reduction in TAV at follow-up coronary CTA in the treatment group, this

TABLE 4 Mean ± SD Coronary CTA Plaque Parameters at Follow-Up and Changes Compared With Baseline in the Control and Treatment Groups

	Control (n = 40)				Treatment (n = 40)			
	Follow-Up (mm ³)	Follow-Up TVV* (%)	Change (%) From Baseline (mm ³)	p Value†	Follow-Up (mm ³)	Follow-Up TVV‡ (%)	Change (%) From Baseline (mm ³)	p Value§
LAPV	32.3 ± 6.2	6.3 ± 1.2	−6.6 (17.0) ± 12.8	0.003	23.0 ± 21.4	5.2 ± 4.8	−15.9 (40.9) ± 17.3	<0.001
DCPV	19.9 ± 9.4	3.9 ± 1.8	−1.6 (7.3) ± 8.3	0.32	18.5 ± 8.4	4.2 ± 1.9	−0.1 (0.5) ± 8.3	0.85
NCPV	166.8 ± 48.2	32.6 ± 9.4	−18.2 (9.8) ± 43.9	0.01	155.3 ± 49.4	34.9 ± 11.1	−26.3 (14.5) ± 55.8	0.005
TAV	219.1 ± 42.3	42.8 ± 8.3	−26.4 (10.8) ± 42.1	<0.001	196.8 ± 41.6	44.2 ± 9.3	−42.3 (17.7) ± 66.6	0.001
TLV	292.5 ± 35.3	57.2 ± 6.9	–	–	248.8 ± 43.8	55.8 ± 9.8	–	–
RI	1.17 ± 0.15	–	−0.01 (0.8) ± 0.11	0.40	1.17 ± 0.13	–	−0.04 (3.2) ± 0.14	0.14

Values are mean ± SD or mean (%) ± SD. *Mean TVV = 511.6 mm³. †Mean TVV = 445.6 mm³. ‡p Values comparing baseline and follow-up values in the †control group and the §treatment group. Abbreviations as in Table 2.

FIGURE 2 Distal Right Coronary Artery Plaque Identified at Baseline

(A) Curved planar reformat; (B) curved planar reformat with color overlay coded image map to identify plaque components; (C to E) representative cross-sectional views with color overlay. **Light blue arrows** indicate low attenuation plaque (**dark blue**); noncalcified plaque, **purple**; dense calcified plaque, **yellow**; lumen **green**. LAP volume = 4.2 mm³, NCP volume = 46.5 mm³, DCP volume = 2.2 mm³, lumen volume = 41.4 mm³. DCP = dense calcified plaque; LAP = low attenuation plaque; NCP = noncalcified plaque.

difference was not statistically significant (treatment: mean 42.3 [−17.7%] ± 66.6 mm³; control: mean 26.4 [−10.8%] ± 42.1 mm³; $p = 0.28$). Similarly, there was no significant difference between cohorts when comparing change in DCPV ($p = 0.66$), NCPV ($p = 0.62$), or remodeling index ($p = 0.36$). Changes in TAV, DCPV, and NCPV as a proportion of TVV (Table 4) also did not differ significantly between treatment and control groups. Finally, there was appropriate and comparable LDL reduction in both groups (treatment: mean 0.44 [−19.0%] ± 0.60 mmol/l; control: mean 0.49 [−20.2%] ± 0.49 mmol/l; $p = 0.21$) (Figure 4C).

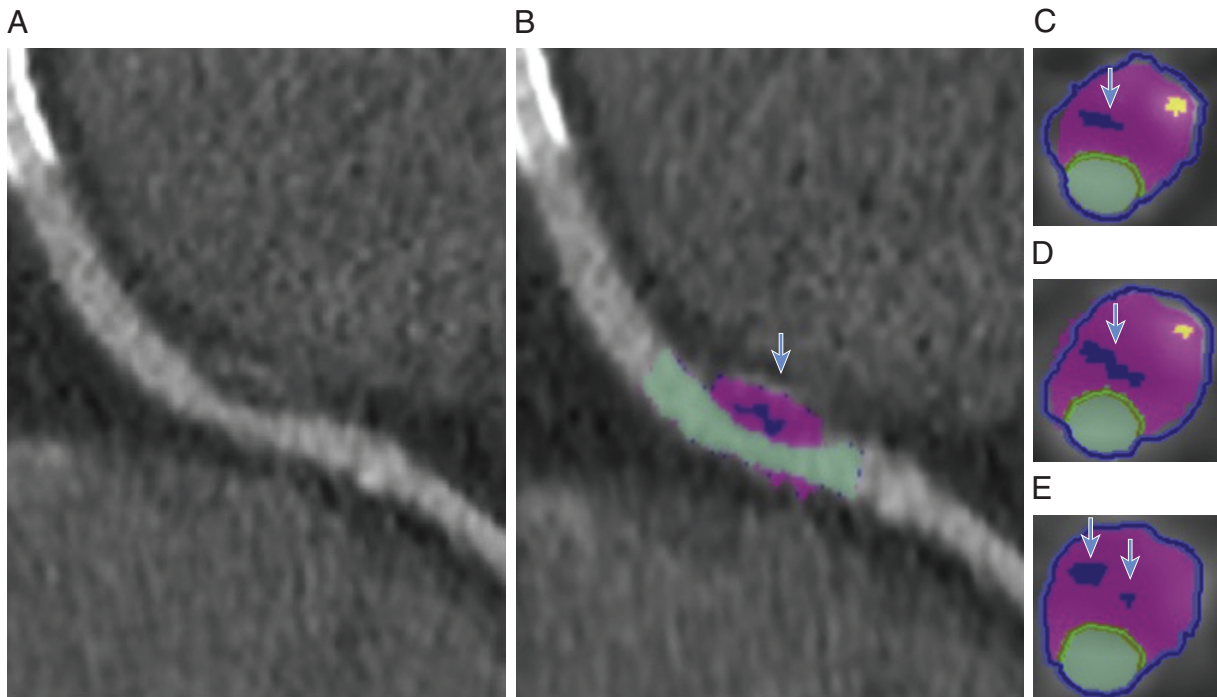
Table 5 shows the multivariate linear regression analysis after adjusting for differences between cohorts and factors that may have influenced outcomes during the follow-up period (see the Methods section). In this multivariate model, colchicine therapy remained significantly associated with reduction in LAPV ($p = 0.039$) and hsCRP ($p = 0.004$) compared with controls, but there was no significant difference between groups for the other outcomes. The partial

R^2 of colchicine therapy was 4.3% and 9.1% for change in LAPV (overall $R^2 = 36.0\%$) and hsCRP (overall $R^2 = 34.6\%$), respectively, indicating that colchicine therapy accounted for a significant proportion of the variance in these outcomes during the follow-up period.

These findings were supported by the statistically significant 2-way interaction effect between treatment group (controls vs. colchicine) and time (baseline vs. follow-up) on LAPV ($p = 0.002$) and hsCRP ($p < 0.001$) (Table 6) alone, with no effect seen for the other outcome variables.

Finally, we examined the linear relationship and strength of correlation between the 2 significant outcome variables (Figure 5A). There was evidence of a highly significant linear relationship ($R^2 = 0.158$; $p < 0.001$) and strong positive correlation ($r = 0.578$) between change in LAPV and change in hsCRP. Similarly, there was a highly significant linear relationship ($R^2 = 0.123$; $p = 0.001$) and moderate positive correlation ($r = 0.417$) between change in LAPV and change in LDL (Figure 5B); however, there was no

FIGURE 3 Distal Right Coronary Artery Plaque Reimaged After 12 Months of Oral Colchicine (0.5 mg/day)



(A) Curved planar reformat; (B) curved planar reformat with color overlay coded image map to identify plaque components; (C to E) representative cross-sectional views with color overlay. See Figure 1 legend for color descriptions. LAPV = 3.2 mm³ (–23.8%), NCPV = 65.8 mm³ (+41.5%), DCPV = 0.3 mm³ (–86.4%), lumen volume = 47.2 mm³ (+14.0%). DCPV = dense calcified plaque volume; LAPV = low attenuation plaque volume; NCPV = noncalcified plaque volume.

relationship between change in hsCRP and change in LDL ($R^2 = 0.047$; $p = 0.06$).

ADVERSE EVENTS. Only 1 patient developed an adverse event resulting from colchicine therapy (gastrointestinal intolerance, particularly diarrhea); colchicine treatment was subsequently ceased by investigators. Two patients had colchicine therapy ceased by their primary physician for unspecified reasons, and 2 were noncompliant with therapy (Figure 1).

There were no deaths or myocardial infarction in either group during the follow-up period. Two patients in the treated cohort underwent cardiac catheterization for investigation of recurrent chest pain but did not undergo percutaneous coronary intervention. One patient in the untreated cohort presented with enzyme-negative unstable angina and underwent percutaneous coronary intervention to a new culprit stenosis.

DISCUSSION

This study demonstrates, for the first time, that regular low-dose colchicine therapy has significantly

greater coronary plaque-stabilizing effects than OMT alone, as evidenced by a significant reduction in both LAPV and hsCRP. These changes were seen in the context of a substantial and similar reduction in LDL in both treatment and control groups, indicative of successful statin intensification therapy post-ACS. Although there was a moderate positive correlation between change in LDL and change in LAP volume suggesting that LDL reduction may have contributed to plaque stabilization, the comparable LDL reduction in both groups suggests that improvements in plaque morphology are not driven solely by changes in LDL, but also by the anti-inflammatory properties of colchicine. This is supported by the substantially larger reduction in hsCRP in the treatment group compared with controls. Furthermore, the significant linear association and strong positive correlation between change in LAPV and change in hsCRP suggests that these 2 processes are related, and that reduction in hsCRP, mediated by colchicine's anti-inflammatory effects, is manifested simultaneously by reduction in the burden of potentially vulnerable coronary plaque.

TABLE 5 Primary and Secondary Outcomes

		Univariate Analysis		Multivariate Analysis			
		n	Change	p Value	B	Model R ²	Partial R ² p Value
LAPV, mm ³	Control	40	-6.6 ± 12.8	0.008	0 (Ref)	0.360	- 0.039
	Treatment	40	-15.9 ± 17.3		0.232		0.043
DCPV, mm ³	Control	40	-1.6 ± 8.3	0.66	0 (Ref)	0.372	- 0.47
	Treatment	40	-0.1 ± 8.3		-0.080		0.005
NCPV, mm ³	Control	40	-18.2 ± 43.9	0.62	0 (Ref)	0.229	- 0.21
	Treatment	40	-26.3 ± 55.8		0.153		0.019
TAV, mm ³	Control	40	-26.4 ± 42.1	0.28	0 (Ref)	0.332	- 0.10
	Treatment	40	-42.3 ± 66.6		0.190		0.029
RI	Control	40	-0.01 ± 0.11	0.36	0 (Ref)	0.133	- 0.16
	Treatment	40	-0.04 ± 0.14		0.184		0.027
hsCRP, mg/l	Control	40	-0.38 ± 1.21	<0.001	0 (Ref)	0.346	- 0.004
	Treatment	39	-1.10 ± 1.15		0.344		0.091
LDL, mmol/l	Control	40	-0.49 ± 0.49	0.21	0 (Ref)	0.539	- 0.48
	Treatment	40	-0.44 ± 0.60		-0.067		0.003

Values are mean ± SD.
β = standardized regression coefficients; other abbreviations as in Tables 2 and 3.

Vulnerable plaques that are prone to rupture are commonly lipid-rich, with a large necrotic core and thin fibrous cap (2,7). These can be identified on coronary CTA based on high-risk features including outward vessel positive remodeling (index >1.1), low attenuation plaque (<30 HU), spotty calcification, and the “napkin ring” sign (a ring of high attenuation around plaque) (6,7). Of these, LAP has consistently been shown to be the strongest marker of instability, which we replicated in our study.

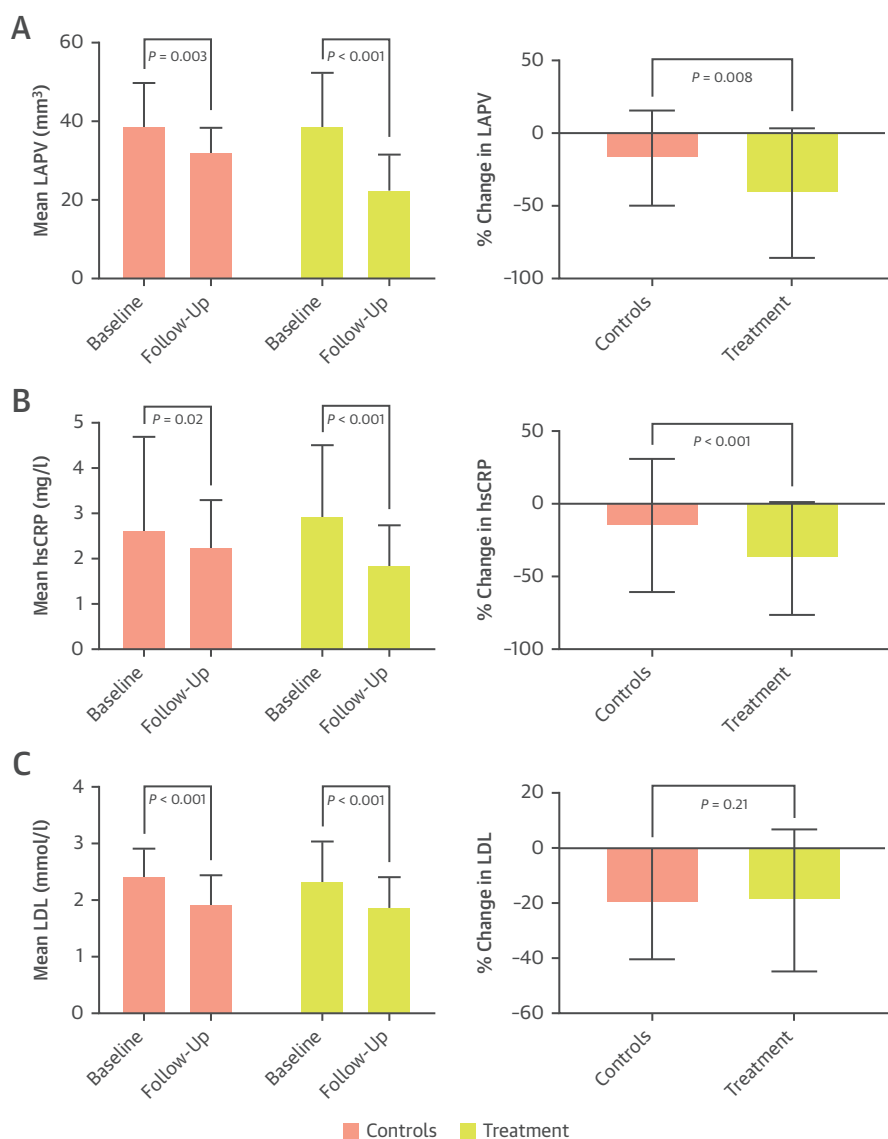
Across 2 large studies (6,13) of more than 1,000 patients each, the presence of LAP on coronary CTA was a powerful independent predictor of ACS and MACE at follow-up, along with positive remodeling and the napkin ring sign. The strong predictive value of LAP as an adverse prognostic indicator has also been demonstrated in an ex vivo study (14) demonstrating an association between the relative area of LAP by quantitative histogram analysis and lipid-rich plaque core. Coronary CTA has also been evaluated against other high-resolution intracoronary imaging modalities, in particular intravascular ultrasound and optical coherence tomography (15). In 2 comparative studies (16,17), vulnerable thin-cap fibroatheroma plaque as assessed by optical coherence tomography

were significantly associated with the presence of LAP on coronary CTA, as well as positive remodeling and napkin ring sign. Two similar comparative studies with intravascular ultrasound (15,18) showed that low-density plaque on coronary CTA correlated significantly with vulnerable plaque with a larger necrotic core plus fibrofatty tissue. One other study (19) has also demonstrated a strong correlation between CT and intravascular ultrasound for positive remodeling indices.

The plaque-stabilizing properties of statins have been evaluated by coronary CTA in several studies to date. Two prospective studies (9,10) have shown that in patients treated with a statin, there was reduced progression or a greater reduction in LAPV and TAV at follow-up compared with controls. Statins are not only highly effective for the treatment of dyslipidemias, but also exert a range of cardioprotective “pleiotropic” effects with anti-inflammatory and antioxidant properties (20). As a result, they have been universally incorporated into clinical guidelines as part of secondary prevention post-ACS. A Cochrane systematic review (20) of 18 randomized control trials (n = 14,303) comparing statin therapy (initiated within 14 days of ACS) with placebo or usual care, found that statin therapy reduced the incidence of unstable angina at 4 months post-ACS (4.8% vs. 6.3%). However, despite a trend toward risk reduction, there was no statistically significant reduction in incidence of mortality (2.5% vs. 2.8%), myocardial infarction (5.9% vs. 6.5%), total stroke, or revascularization procedures at 4 months of follow-up. These findings support the need for further agents for secondary prevention post-ACS, and colchicine may be an attractive option to serve this need via further plaque stabilization.

Indirect support for a beneficial effect of colchicine comes from 2 retrospective studies that showed reduced CVD incidence in patients with continuous colchicine use for the treatment of gout (21) and familial Mediterranean fever (22). A 2013 randomized controlled trial (LoDoCo [Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease]) of 532 patients (23) with stable coronary artery disease (CAD) followed over a median of 3 years showed that colchicine 0.5 mg/day administered in addition to high-dose statin therapy and OMT was highly effective in the prevention of nonstent-related ACS compared with placebo. This trial hypothesized these beneficial effects of colchicine were due to its ability to suppress levels of inflammatory mediators and prevent cholesterol crystal-induced neutrophil-mediated inflammation implicated in atherosclerosis. Finally, a 2015

FIGURE 4 Primary and Secondary Outcomes



(A) Mean LAPV at baseline and follow-up, and % change in LAPV, in control and treatment groups. (B) Mean hsCRP at baseline and follow-up, and % change in hsCRP, in control and treatment groups. (C) Mean LDL at baseline and follow-up, and % change in LDL, in control and treatment groups. hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; other abbreviation as in Figure 3.

meta-analysis (5) of 1,301 patients in 5 randomized controlled trials showed that colchicine was associated with a >50% reduction in the composite CV outcome that included CAD, ACS, stroke, revascularization, and stable congestive cardiac failure.

Our group has explored several pathophysiological mechanisms potentially explaining the atheroprotective properties of colchicine (3,4). Exposure of

neutrophils and monocytes/macrophages to various stimuli (including cholesterol crystals) in atherosclerotic plaque triggers NLRP3 inflammasome activation, which is a cytosolic multiprotein complex that promotes caspase-1-dependent interleukin (IL)-1 β and IL-18 secretion (24). Caspase-1 levels strongly correlate with CV events in CAD patients, and IL-1 β and IL-18 are both key inflammatory cytokines that, like

TABLE 6 2-Way Mixed ANOVA Repeated Measures Testing for Interaction Between Treatment Group (Controls vs. Colchicine) and Time (Baseline vs. Follow-Up) on Primary and Secondary Outcome Variables

	n	F	p Value
LAPV	80	11.608	0.002
DCPV	80	0.659	0.42
NCPV	80	0.415	0.52
TAV	80	1.583	0.22
RI	80	0.881	0.35
hsCRP	79	18.398	<0.001
LDL	80	0.184	0.67

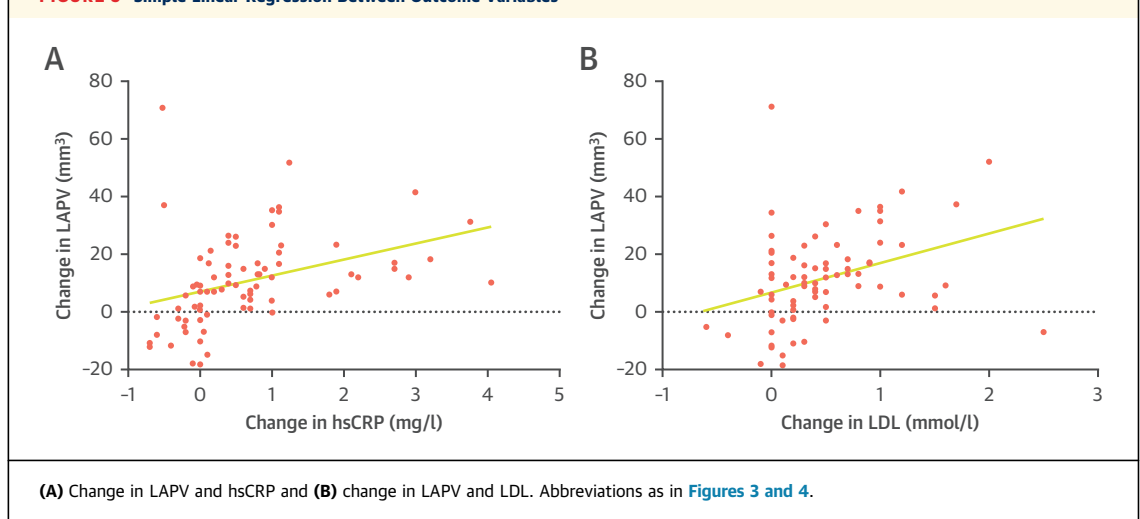
ANOVA = analysis of variance; other abbreviations as in Tables 2 and 3.

downstream IL-6, are implicated in plaque development, progression, and destabilization. We have demonstrated that in patients with ACS, there is evidence of monocyte inflammasome activation (4) with higher transcoronary gradients of IL-1 β , IL-18, and IL-6 compared with controls (3) and that short-term oral colchicine suppresses monocyte secretion of IL-1 β , via caspase-1 inhibition, as well as reducing transcoronary inflammasome-related cytokine gradients (3). Similar to previous studies (25), colchicine also resulted in a significant reduction in hsCRP, a cytokine synthesized in response to IL-6 release from activated monocytes. hsCRP is an inflammatory biomarker that has been credited as a potential predictive tool for screening, risk classification, and assessment of response to therapy in CVD. A hsCRP level >3 mg/l is independently associated with a 60% excess risk of incident CAD compared with levels <1 mg/l after adjusting for other risk factors (26).

Furthermore, the landmark JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial (27) showed that statin therapy as primary prevention in patients with a low LDL but high hsCRP yielded a robust 44% reduction in risk of MACE compared with placebo. This reduction was substantially higher than expected from previous statin trials evaluating the effect of LDL reduction on MACE, suggesting that hsCRP reduction is more predictive of better outcomes than LDL reduction alone. Our study has reaffirmed the observation that reduction in hsCRP translates into favorable plaque modification independent of LDL change.

STUDY LIMITATIONS. The present study has some limitations, including a relatively small sample size and short-term follow-up (12 months) for repeat coronary CTA and serum biomarkers. Coronary CTA plaque assessment was performed by multiple experienced reporters, and although this semiautomated process was prone to the possibility of individual errors in plaque evaluation, we found very little interobserver variability (see the Methods section). However, intraobserver variability and scan-rescan repeatability were not assessed. Furthermore, in this prospective nonrandomized observational study, we were unable to perform an intention-to-treat analysis on any patients in the treatment arm who discontinued participation during the study period because they did not present for or consent to a follow-up coronary CTA. Despite the lack of randomized data, the 2 groups (treatment vs. controls) were quite well matched, with differences at baseline seen in only 1 clinical variable (statin use). There were

FIGURE 5 Simple Linear Regression Between Outcome Variables



no differences between groups in baseline coronary CTA parameters or biochemical variables. We operated a multivariate linear regression analysis to account for differences between groups, with no substantial change in p value of significance. Interestingly, statin use was lower in the treatment group, and the improved plaque morphology in this group (compared with controls) despite this implies that this effect was not mediated by differences in statin therapy. Finally, this study was not adequately powered to evaluate clinically significant endpoints such as adverse CV events and mortality.

CONCLUSIONS

This present study demonstrates, for the first time, that low-dose colchicine favorably modifies potentially vulnerable coronary plaque. The knowledge that atherosclerosis is an inflammatory disease offers new opportunities for the prevention and treatment of coronary artery disease. Accordingly, a synergistic strategy of colchicine plus statin could fundamentally shift approaches to atherosclerosis modulation.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Low-dose colchicine plus optimal medical therapy favorably modifies potentially vulnerable coronary plaque compared with optimal medical therapy alone, as assessed by coronary CTA. These improvements in plaque morphology are likely driven by the anti-inflammatory properties of colchicine.

TRANSLATIONAL OUTLOOK: Colchicine may represent a valuable therapeutic tool to add to the armament of currently available secondary prevention options. Additional large, randomized clinical trials are required to evaluate whether low-dose colchicine therapy results in lower rates of future adverse cardiovascular events.

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KEY WORDS acute coronary syndrome, atherosclerosis, colchicine, coronary artery disease, CT coronary angiography, inflammation